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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/810,310	03/14/2001	Samir Khleif	15280415100	9099

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/810,310	Samir et al.
Examiner	**Art Unit**
DiBrino, Marianne	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 21, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above, claim(s) *3-5, 9, 10, and 18-31* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 6-8, and 11-17* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment and response filed 10/21/02 (Paper No. 4) is acknowledged and has been entered.

2. Applicant's election with traverse of Group II (claims 1, 2 and 6-17), and species of HPV E7 antigen and B7-1 as the costimulatory molecule in Paper No. 4 is acknowledged.

The **traversal is on the ground** that the restriction does not constitute undue burden as balanced against the right of Applicant to claim the invention and to provide for a compact and expedited prosecution. Applicant's argument has been considered, but is not deemed persuasive for the following reasons. Regarding applicants comments about undue burden, the M.P.E.P. § 803 (July 1998) states that: "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The restriction requirement enunciated in the previous Office Action meets this criterion and therefore establishes that serious burden is placed on the Examiner by the examinational Groups. In addition, The inventions are distinct for reasons elaborated in paragraphs 3-7 of the previous Office Action.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 2, 6-8 and 11-17 read on the elected species, HPV E7 antigen and costimulatory molecule B7-1..

Accordingly, claims 9 and 10 (non-elected species of Group II) and claims 3-5 and 18-31 (non-elected groups I, III and IV) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1, 2, 6-8 and 11-17 are currently being examined.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the inventors' addresses and post office addresses are not given.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Applicant is advised that the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999 were published subsequent to the prior Office Action and the claims have been examined in view of these guidelines. The following rejection is set forth herein.

Claim 1, 2, 6-8 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed method for eliciting an immune response in a subject comprising administering a peptide or protein antigen comprising one or more T cell epitopes coordinatedly with a non-viral vector encoding a costimulatory molecule, including those antigens, polynucleotides and vectors such as naked DNA vector, recited in the instant claims.

The instant claims encompass a method of gene therapy. There is insufficient disclosure in the specification on such a method as claimed in the instant claims.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

The specification discloses immunizing mice with a peptide antigen emulsion, i.e., an HPV E7 peptide, followed by an intradermal injection of B7-encoding DNA plasmid vector (especially Example 1). The specification further discloses measuring CTL extracted, i.e., ex vivo, from the said mice for immunoreactivity to the E7 immunizing peptide and an increased effect when B7-encoding DNA plasmid vector was coordinately administered with the peptide antigen. The instant specification does not disclose treatment of subjects with peptide antigens other

than the aforementioned HPV E7 peptide antigen and a non-viral vector encoding a costimulatory molecule other than B7.1.

There are insufficient relevant identifying characteristics disclosed.

6. Claims 1, 2, 6-8 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The specification does not disclose how to elicit an immune response in a subject comprising administering a peptide or protein antigen comprising one or more T cell epitopes coordinatedly with a non-viral vector comprising a polynucleotide encoding a T cell co-stimulatory molecule, including those antigens, polynucleotides and vectors such as naked DNA vector, recited in the instant claims. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a method of gene therapy. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can be used.

The specification discloses immunizing mice with a peptide antigen emulsion, i.e., an HPV E7 peptide, followed by an intradermal injection of B7-encoding DNA plasmid vector (especially Example 1). The specification further discloses measuring CTL extracted, i.e., ex vivo, from the said mice for immunoreacitvity to the E7 immunizing peptide and an increased effect when B7-encoding DNA plasmid vector was coordinately administered with the peptide antigen.

Gene therapy has been largely ineffective and has induced mortality, as evidenced by Nelson et al (Washington Post Jan. 31, 2000 "Earlier Gene Test Deaths Not Reported; NIH Was Unaware of 'Adverse Events'"). Nelson et al teach that gene therapy is a field of experimental medicine that aims to cure diseases by changing people's genetic makeup, but has yet to provide a cure after 10 years of studies on thousands of patients (lines 28-29). Nelson et al further teach that reports of 691 serious adverse events in gene therapy experiments swamped the NIH (lines 15-16) after the death of a patient receiving gene therapy. "That raises the spector that Gelsinger was not the first person to be killed by gene therapy..." (Lines 25-26). Nelson et al (Wash. Post, May 25, 2000, page A01) teaches that University of Pennsylvania, which has been an international leader in the cutting-edge field of medical research, will no longer experiment on people (lines 1-3) ...and (UPenn) would "refocus our efforts in the preclinical area--with the goal of developing a foundation of science necessary to ensure the ultimate success of this field. Although numerous scientific obstacles exist, gene therapy has tremendous potential to someday prevent or cure life-threatening diseases." (Lines 21-24).

There is insufficient guidance in the specification as to how to practice the method of the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 15 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 15 is indefinite in the recitation of "proximal target sites selected from the same, or closely-adjacent...sites" because it is not clear what is meant, and closely-adjacent is a relative term.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 2, 6-8 and 11-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,738,852 in view of WO 98/04705 (document and CAPLUS Accession No. 1998: 106018 summary of document) and Kaufmann et al (Cell. Immunol. 1996, 169/2 246-251).

U.S. Patent No. 5,738,852 discloses inducing partial immunity by administering recombinant polynucleotides, including in the form of non-viral vectors or naked DNA or RNA operably linked to regulatory elements for expression, encoding immunostimulatory factor such as B7.1 and/or a target antigen polypeptide from a viral protein (entire document, especially Abstract, claims, column 4 at lines 45-67, column 6 at lines 31-32, column 9 at lines 40-46, column 10 at lines 36-46, column 13 at lines 41-67. U.S. Patent No. 5,738,852 discloses administration

by any suitable means known in the art including by parenteral means, i.e., such as "subcutaneous" recited in instant claim 15. U.S. Patent No. 5,738,852 discloses that separate polynucleotides can encode the antigenic polypeptide and the costimulatory molecule, each is are mixed with a suitable excipient and the number and timing of doses is determined by routine methods known to those of skill in the art.

U.S. Patent No. 5,738,852 does not disclose administering the viral antigen as a peptide or protein antigen coordinately with the polynucleotide encoding the costimulatory molecule and does not disclose a viral antigen from HPV.

WO 98/04705 and the CAPLUS Accession No. 1998: 106018 summary of the said document teach a pharmaceutical composition for treating a HPV infection comprising HPV E7 polypeptides and a costimulatory molecule B7.1 or a recombinant vector encoding the polypeptides.

Kaufman et al teach that HPV E7 expressing cells fail to induce an effective CTL response due to a lack of expression of costimulatory molecules such as CD80 (B7.1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered the viral polypeptide(s) including the HPV E7 polypeptide taught by Kaufman et al and a costimulatory molecule, such as B7.1 taught by Kaufman et al, U.S. Patent No. 5,738,852 and WO 98/04705 and the CAPLUS Accession No. 1998: 106018, as recombinant polynucleotides as disclosed by U.S. Patent No. 5,738,852 or as polypeptides as taught by WO 98/04705 and the CAPLUS Accession No. 1998: 106018 or as combination of polypeptide antigen and polynucleotide encoding costimulatory molecule or visa versa. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered the viral polypeptide(s) either simultaneously or sequentially with the polynucleotide encoding the costimulatory molecule.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because U.S. Patent No. 5,738,852 discloses that the vaccines can be administered as polynucleotides and WO 98/04705 and the CAPLUS Accession No. 1998: 106018 teach that the vaccines can be disclosed as either polynucleotides or as peptides to achieve the common function of eliciting immunity to the viral polypeptide(s). In addition, Kaufman teaches that response to HPV E7 polypeptide antigen requires expression of costimulatory molecule B7.1. One of ordinary skill in the art at the time the invention was made would have been motivated to administer simultaneously or sequentially depending upon the excipients required for the antigen and the costimulatory molecule or the amounts required per dosage.

The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Section MPEP 2144.07.

It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Instant claim 15 is included in this rejection because it would have been prima facie obvious at the time the invention was made to have administered the antigen and polynucleotide "to proximal target sites selected from the same, or closely adjacent...sites" depending upon what route was desired. In addition, the limitation "closely adjacent" can be broadly interpreted to read on sites of undetermined distance.

12. No claim is allowed.

13. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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January 16, 2003

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